

REMARKS

This Amendment is in reply to the Office Action mailed June 27, 2006. Applicants have reviewed the Office Action and have the following comments.

Claim 16 has been amended to increase its clarity; the amendment is not a narrowing amendment and does not affect the scope of equivalents in any way. No new matter was added by way of this amendment.

Rejection Pursuant to 35 U.S.C. §103(a)

1) Initial Comments

The Office Action of June 27th, 2006 (the "Office Action") maintains the rejection of pending claims 16, 18-22 and 30 as being allegedly obvious over U.S. Patent Application 2002/0040015, to Miller et al., in view first of Granville, (U.S. Patent No. 6,180,402), and further in view of Wheeler et al., EUR. J. OPHTHAL. 9:S17-S21 (Jan-Mar 1999). Applicants traverse this rejection.

Applicants strongly believe that the rejection of the pending claims is in error and therefore respectfully incorporate by reference the arguments made in the Amendment filed April 3, 2006 in favor of the patentability of these claims.

In addition, Applicants respectfully take issue with the assertion, contained in the Office Action when discussing the non-obviousness of the claims, that the April 3rd Reply only responded to the cited references individually and failed to respond to

their combination. Applicants note that beginning on page 8, last paragraph of that Office Action the effect of the combination of all cited art was discussed. Applicants also point out that the suggestions of each reference must individually be extracted and discussed before the effect of their combination can be ascertained. For purposes of clarity Applicants have the following further comments.

2) Rebuttal to the Office Action's Characterization of the Cited References.

The June 27th Office Action alleges "considering what was known in the art, *as a whole*," the present invention is *prima facie* obvious. Office Action, page 6. (emphasis in original). However, the issue is not whether "what was known in the art" is considered as a whole, but whether the disclosure and suggestions of each prior art reference, and their combination, is so considered. The Court of Customs and Patent Appeals stated, and the Federal Circuit has often reiterated, "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 147 USPQ 391 (CCPA 1965).

The June 27th 2006 Office Action fails to characterize the teachings of the prior art references completely, or entirely accurately. For example, the Office Action says Miller teaches "the general state of the art with respect to photodynamic therapy (PDT) to treat conditions of the eye, including choroidal neovascularization using PDT", and further stated "Miller,

however is silent with regard to using agents to ameliorate the adverse effects of PDT" Office Action page 6. The Office characterizes Granville as teaching that it is beneficial to add an anti-apoptotic molecule in PDT to ameliorate the adverse effects of PDT or to enhance the selectivity of PDT. *Id.* Wheeler is said to teach that brimonidine is an anti-apoptotic neuroprotectant, and the present application is said to acknowledge that "PDT can result in optic nerve atrophy." *Id.* Applicants believe that these references have neither been considered entirely accurately or analyzed for the entirety of that they teach or suggest.

First, contrary to the Examiner's contention, Miller does in fact discuss amelioration of adverse effects of PDT. On page 11 of the provisional patent application Miller states that different apoptotic pathways are triggered by PDT in bovine retinal capillary endothelial (BRCE) and retinal pigment epithelium (RPE) cells. Miller continues "it may be possible to specifically prime the apoptotic machinery of neovascular endothelial cells prior to PDT so as to increase their sensitivity to PDT. . . . This approach could reduce the light dose (fluence) necessary to achieve CNV closure and thereby decrease the effect on the surrounding cells such as RPE." '015 application at page 11.

This statement suggests that cells of the same basic "type" (BRCE and RPE endothelial cells) have such different susceptibility to apoptosis that one may differentially utilize PDT to kill one without harming the other.

In other words, far from being silent with regard to the treatment of adverse effects, Miller (like Granville), teaches

that apoptosis is a cell-specific phenomenon and suggests taking advantage of this discrepancy between different cell types' susceptibility to apoptosis triggered by PDT.

Miller is silent with regard to neural cells or neuroprotection.

Second, while Granville does indeed disclose the use of anti-apoptosis agents in conjunction with PDT to treat "adverse effects" of PDT, Granville never discusses what these adverse effects are. Granville never suggests the use of a neuroprotectant generally or protecting neural cells specifically. Rather, the examples of Granville are entirely concerned with loading blood cells with anti-apoptotic CPP32 protease inhibitors prior to PDT, and 2) observing a decrease in apoptosis of these blood cells following PDT. This probably because Granville is mainly concerned with protecting blood cells from destruction in tumor-targeted PDT, with which the Granville reference is more concerned.

Like Miller, Granville cautions "inhibition of apoptosis is also target cell dependent." Granville, column 3, line 4.

Third, it is true that the present application discloses at page 3 that it was known that long-term optic nerve atrophy was seen with the use of the photosensitizer vertporfin. However, the application makes clear that this effect was observed "at high doses" of the photosensitizer (12 and 18 mg/m³). No mention is made of retinal ganglion cells.

Fourth, Wheeler discloses that brimonidine is a neuroprotectant and that it enhances retinal ganglion cell

survival in models of retinal nerve cell injury, and may do so partly through the induction of anti-apoptotic genes such as bcl-2 and neuronal survival factors such as bFGF. Wheeler does not indicate that brimonidine is effective to treat optic nerve atrophy or mention or even suggest photodynamic therapy.

As set forth in the Reply of April 3, 2006, a finding of *prima facie* obviousness requires 1) evidence of a suggestion or motivation to modify or combine the references, 2) a reasonable expectation of success if the suggestions were followed, and 3) that all claim limitations are found in the prior art. See e.g., MANUAL OF PATENT EXAMINING PROCEDURE §2142 at 2100-134 (8th Ed., Rev. 4, 2006) (hereinafter "MPEP"); see also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Applicants appreciate and acknowledge the Examiner's agreement on page 5 of the June 27, 2006 Office Action that this is the required legal standard.

With respect to these requirements, Applicants respectfully submit that the Office Action attempts to make out a *prima facie* case based upon a hindsight-based "pick and choose" analysis to the present claims. Essentially the Office Action's rationale appears to be that A can be found in Miller, A and B in Granville, and C in Wheeler; therefore it would have been obvious to combine the references to make A + B + C, which it alleges is the claimed invention, with a reasonable expectation of success. However, even putting all else aside, the Office Action does not indicate why, knowing from Miller and Granville that sensitivity and resistance to apoptosis is cell specific, a person of ordinary skill in the art would have the motivation to combine these references to conceive the present invention with a reasonable expectation of success if the invention were reduced to practice.

Nor does the combination of these references teach every limitation of the rejected claims. Claim 16 is drawn to a method of protecting ocular neural tissue from damage caused by PDT comprising delivering an amount of brimonidine effective to protect a plurality of ocular neurons from damage as compared to the degree of ocular neuron cell death observed in the absence of said amount of brimonidine. The combined references do not teach this comparative step. Claim is drawn to intraocular injection of this amount of brimonidine, such limitation is nowhere to be seen.

Claim 21 is drawn to subretinal injection, which is completely absent from the cited art, as is intravitreal injection (claim 22). Claim 30 is drawn to a combination of brimonidine and an anti-angiogenic compound for use in a method of combination therapy with PDT; the examiner has not pointed out where these limitations can be found; Applicants respectfully submit that they are absent therefrom.

Thus, Applicant believe no *prima facie* case of obviousness has been or can be established against the present claims. The Office Action employs hindsight in choosing the components of the composition used in the claimed methods from amongst the prior art, then combining these elements in an attempt to "make" this invention.

The Court of Appeals for the Federal Circuit has repeatedly warned "[c]are must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'" *Grain Processing*

Corp. v. American Maize-Products Co., 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988) (citation omitted); see also *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). Respectfully, Applicants believe that this is what has inadvertently happened in the present case.

Additionally, the Miller reference actually teaches away from the present invention, since its solution to prevent harm to surrounding cells is to sensitize the target cells to apoptosis while reducing the fluence of the laser. Use of an apoptosis antagonist is not even entertained by the Miller application.

Finally, even assuming *arguendo* that the combined references were to be found to suggest attempting the present invention, this is not sufficient; "obvious to try" is not the same as "obvious", i.e., having a reasonable expectation of success. There could have been no reasonable expectation of success in the present case, since it is not clear that the problem solved by the present invention was recognized by the prior art (i.e., the prior art does not indicate that PDT at less than "high doses" of photosensitizer, or using a different photosensitizer than vertiporfin, harms any ocular neural tissue), or than, once recognized treatment with brimonidine would be effective (since Granville teaches that inhibition of apoptosis is target cell dependent and Miller teaches that different cells, even of the same lineage such as epithelial cells) are differently susceptible to apoptosis.


For these reasons the Applicants respectfully request reconsideration and withdrawal of the present rejections.

CONCLUSION

For the reasons given above, the claims are now thought to be in condition for allowance, and a Notice to that effect is earnestly sought.

No fee is thought due in connection with this communication. However, if Applicants are in error with regard to this point, please use Deposit Account 01-0885 for the payment of any such fee now due, or to credit any overpayment.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Carlos A. Fisher', written in a cursive style.

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